REMARKS

The subject matter claimed relates in part to methods for predicting the likelihood of a subsequent cerebral vasospasm in patients presenting with subarachnoid hemorrhage.

Claim 14 is canceled herein without prejudice or disclaimer. Applicants expressly reserve the right to prosecute claims having the subject matter of claim 14 in this or other related applications. Claims 1, 5, 8, 11, 15, 16, and 18, 21, 25, and 26 are amended herein to expedite allowance of the application, to correct grammatical errors, and to make the language of dependent claims agree with claims from which they depend. No new matter is added to the amended claims. Claims 27-29 are newly added. Claims 27-29 find support in the specification as filed, for example, at least in paragraph [0022] on page 7 and Example 4 of the specification as filed. No new matter is added by the claim amendments and new claims, and their entry is respectfully requested.

Applicants request reconsideration of the claimed invention in view of the amendments and following remarks.

35 U.S.C. §112, Second Paragraph

Claims 1, 5, 8, 11, 14-16, and 18-26 stand rejected as allegedly failing to satisfy the definiteness standard of 35 U.S.C. §112, second paragraph. Applicants do not agree that the claims are indefinite. However, to advance prosecution, and not in acquiescence to the rejection, applicants have amended claim 1 to remove the language "said plurality of markers are independently selected from the group consisting of specific markers of neural tissue injury, markers related to blood pressure regulation, markers related to inflammation, and markers related to apoptosis". Claim 14 is canceled herein. Applicants respectfully submit that the rejection of claims 1, 5, 8, 11, 14-16, and 18-26 as allegedly failing to satisfy the definiteness standard of 35 U.S.C. §112, second paragraph is now moot, and respectfully request that the rejection be withdrawn.

35 U.S.C. §102

I. Claims 1, 14, 16, and 19-21 have been rejected as allegedly anticipated by Sviri *et al., Stroke* 31: 118-122, 2000. Applicants assert that claim 1 is novel with respect to Sviri *et al.*. Solely to advance prosecution, Applicants have amended claim 1 such that claim now recites:

> A method of characterizing a risk of future cerebral vasospasm in a subject suffering from a subarachnoid hemorrhage, comprising:
>
> determining the presence or amount of a plurality of subject-derived markers in a sample obtained from said subject, wherein one or more of said subject-derived markers are selected from the group consisting of neural cell adhesion molecule (NCAM), vascular endothelial growth factor (VEGF), matrix metalloprotease-9 (MMP-9), caspase-3, and von Willebrand factor (vWF), or markers related thereto; and
>
> correlating the presence or amount of said plurality of markers to said risk of a future cerebral vasospasm in said subject.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference" *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). [MPEP 2131] Sviri *et al.* do not disclose determining the presence or amount of any of neural cell adhesion molecule (NCAM), vascular endothelial growth factor (VEGF), matrix metalloprotease-9 (MMP-9), caspase-3, and von Willebrand factor (vWF), or markers related thereto, as recited in claim 1 as amended. Nor does Sviri disclose correlating the presence or amount of a plurality of markers that includes any of NCAM, VEGF, MMP-9, caspase-3, or vWF to a risk of future cerebral vasospasm in a patient who has suffered a subarachnoid hemorrhage.

In not disclosing each and every element of claim 1, Sviri *et al.* fails to anticipate claim 1 and claims 16 and 19-21 that depend from claim 1. Claim 14 is canceled herein, rendering its rejection moot. Applicants therefore respectfully request that the rejection under 35 U.S.C. §102(b) be removed.

35 U.S.C. §103(a)

II. Claims 22-24 have been rejected as allegedly unpatentable under 35 U.S.C. § 103(a) over Sviri *et al.* in view of Jackowski, WO00/52476. To advance prosecution, and not in acquiescence to the rejection, Applicants have amended claim 1, from which claims 22-24 depend. Applicants assert that claims 22-24 are nonobvious with respect to the cited references for at least the following reasons.

When making a rejection based on obviousness, the Examiner must ascertain the differences between the claimed invention and the prior art. The asserted combination of the cited references must also teach or suggest *each and every claim feature. See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) (emphasis added) (to establish *prima facie* obviousness of a claimed invention, all the claim features must be taught or suggested by the prior art). The Board of Patent Appeal and Interferences has recently confirmed that a proper obviousness determination requires that an Examiner make "a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art." *See In re Wada and Murphy*, Appeal 2007-3733, decided January 14, 2008, *citing In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis in original), and the MPEP at § 2143.03 provides: "All words in a claim must be considered in judging the patentability of that claim against the prior art. *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)." Applicants further emphasize that the Supreme Court in *KSR Int'l v. Teleflex Inc.* stated that "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

Neither Sviri *et al.* nor Jackowski, cited in the rejection of claims 22-24, disclose determining the presence or amount of any of neural cell adhesion molecule (NCAM), vascular endothelial growth factor (VEGF), matrix metalloprotease-9 (MMP-9), caspase-3, and von Willebrand factor (vWF), or markers related thereto, as recited in claim 1 as amended and incorporated in claims 22-24. Nor do Sviri et al. or Jackowski, alone or in combination, disclose

or suggest correlating the presence or amount of a plurality of markers that includes any of NCAM, VEGF, MMP-9, caspase-3, or vWF for determining the risk of a future cerebral vasospasm in a subject who has suffered a subarachnoid hemorrhage.

Because the Sviri *et al.* and Jackowski fail to teach or suggest all of the elements of claims 22-24, the claims are nonobvious with respect to the cited references, and Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be removed.

III. Applicants respectfully traverse the rejection of claims 5 and 15 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sviri *et al.*, discussed above, in view of Ronn *et al.*, WO00/18801. To expedite prosecution, and not in acquiescence to the rejection, Applicants have amended claim 1, from which claims 5 and 15 depend. Applicants assert that claims 5 and 15 are nonobvious with respect to the cited references for at least the following reasons.

As provided immediately above, a rejection based on 35 U.S.C. § 103(a) requires that each and every claim feature be taught or suggested by the prior art. Applicants assert that neither Sviri *et al.* nor Ronn *et al.* disclose or suggest correlating the presence or amount of a plurality of markers that includes NCAM to a risk of a future cerebral vasospasm in a subject who suffering from a subarachnoid hemorrhage, as provided in claim 1 as amended, from which claims 5 and 15 depend.

Sviri *et al.* does not disclose detecting the presence or amount of NCAM, nor does Sviri *et al.* disclose or suggest correlating the presence or amount of a plurality of markers that includes NCAM with a risk of cerebral vasospasm following subarachnoid hemorrhage.

Applicants disagree that Ronn *et al.* discloses the use of NCAM as a marker of "several disorders including stroke" as stated in the Office Action (Office Action, page 7). The passages referred to in the Office Action suggest that *NCAM-binding compounds* (e.g., peptides), can be used *therapeutically*. Ronn *et al.* does not teach the use of NCAM as a marker for any condition, does not mention diagnosis of any conditions or disease states, does not disclose assessing the

risk of cerebral vasospasm following subarachnoid hemorrhage, and certainly does not contain disclosure of correlating the presence or amount of any marker, including NCAM, with the risk of cerebral vasospasm following subarachnoid hemorrhage, as provided in the claims. Applicants respectfully submit that because the cited references do not disclose all elements of claim 1, from which claims 5 and 15 depend, no prima facie case of obviousness has been established. Applicants therefore respectfully request that the rejection be withdrawn.

IV. Applicants respectfully traverse the rejection of claims 8 and 15 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sviri et al., discussed above, in view of Yakolev et al., J. Neurosci. 17: 7415-24, 1997. Applicants submit that the requirements for a rejection based on obviousness have not been met for at least the following reasons.

An obviousness rejection requires that an Examiner make "a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art." *See In re Wada and Murphy*, Appeal 2007-3733, decided January 14, 2008, *citing In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis in original). Moreover, "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

Sviri *et al.* does not disclose or suggest correlating the presence or amount of a plurality of markers that includes caspase-3 for determining the risk of a future cerebral vasospasm in a subject who has suffered a subarachnoid hemorrhage, as provided in claim 1, from which claims 8 and 15 depend. Yakolev *et al.* does not make up for the deficiencies of Sviri *et al.*, in that Yakolev *et al.* also does not disclose or suggest correlating a plurality of markers that includes caspase-3 with the risk of cerebral vasospasm after subarachnoid hemorrhage, as recited in the claims.

Nor is any rational basis provided for using a plurality of markers that includes caspase-3 to assign a risk of <u>future</u> cerebral vasospasm in a subject that has suffered subarachnoid hemorrhage. The Office Action states that Yakolev *et al.* provides that "caspase-3 levels were

elevated in brain injury" (Office Action, page 8), and that the claimed invention would be obvious "because Yakolev *et al.* taught that caspase-3 levels were elevated in brain injury and the inhibition of caspase-3 markedly attenuates [traumatic brain injury] in vivo and improved neurological recovery" (Office Action, page 8). Applicants assert that elevation of a marker following traumatic brain injury, inhibition of expression of caspase-3 for attenuation of brain injury, and improvement of recovery after traumatic brain injury are not relevant to the claimed subject matter, which concerns assessing the risk of future cerebral vasospasm following subarachnoid hemorrhage by detecting a plurality of markers that includes caspase-3. No rational underpinning for carrying out the claimed invention is provided.

As all the features of claim 1 are not present in Sviri *et al.* or Yakolev *et al.*, alone or in combination, and no rationale for arriving at the claimed invention is present, a case for obviousness has not been made. Applicants therefore respectfully request that the rejection of claims 8 and 15 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

V. Applicants respectfully traverse the rejection of claims 11 and 15 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sviri *et al.*, discussed above, in view of Greenberg, *Drug News and Perspectives* 11: 265-70, 1998. Applicants respectfully submit that the conditions for a rejection based on obviousness have not been met.

An obviousness rejection requires that an Examiner make "a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art." *See In re Wada and Murphy*, Appeal 2007-3733, decided January 14, 2008, *citing In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis in original). Moreover, "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

Sviri *et al.* does not disclose or suggest correlating the presence or amount of a plurality of markers that includes VEGF for determining the risk of a future cerebral vasospasm in a

subject who has suffered a subarachnoid hemorrhage, as provided in claim 1, from which claims 11 and 15 depend. Greenberg does not remedy the deficiencies of Sviri *et al.*, in that Greenberg also fails to disclose or suggest the detection of a plurality of markers that includes VEGF, has nothing to say about the risk of vasospasm following cerebral hemorrhage, and does not disclose correlating the presence or amount of a plurality of markers to a risk of a future cerebral vasospasm in subject that has suffered subarachnoid hemorrhage, as required by the claims.

Applicants respectfully submit that statements in the Office Action that the Greenberg abstract discloses that "stroke results from focal cerebral ischemia due to the occlusion of cerebral blood vessels (angiogenesis) . . ." and "Greenberg taught that VEGF is a key mediator of angiogenesis and cerebral ischemia." (Office Action, page 9) are incorrect. The abstract in fact states ". . . where ischemia is chronic or intermittent, collateral circulation may develop by enlargement of preexisting anastomotic channels or sprouting of new capillaries from existing vessels (angiogenesis)." And while the abstract states that VEGF is "a key mediator of *angiogenesis*", there is no statement in the cited reference to indicate that VEGF is a mediator of cerebral ischemia, as the Office Action states. The Office Action further states: "The understanding of VEGF may have implications for prognosis and treatment in stroke." This statement has no bearing on the claimed invention, as the invention is not drawn to understanding VEGF. Rather, the invention is drawn to assessing the risk of future cerebral vasospasm in a subject suffering from subarachnoid hemorrhage.

Because all features of the claimed invention are not present in the cited references, and no rationale for the claimed invention is present, Applicants respectfully request that the rejection of claims 11 and 15 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

VI. Applicants respectfully traverse the rejection of claim 18 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sviri *et al.*, discussed above, in view of each of Greenberg, Ronn *et al.*, and Yakolev *et al.*, also discussed above. Applicants submit that for the reasons provided in III, IV, and V, above, the cited references do not provide all features of the claims, and further, no rationale is present for providing the claimed invention.

None of Sviri *et al.*, Greenberg, Ronn *et al.*, and Yakolev *et al.*, provide any teaching of correlating the presence or amount of a plurality of markers that includes NCAM, VEGF, and caspase-3 with a risk of a future cerebral vasospasm in a subject who has suffered a subarachnoid hemorrhage, as set forth in claim 18.

The references also fail to provide a rational basis for concluding that the claimed invention is obvious. The Office Action states that "each of the claimed markers has been shown to have relevance in the measurement of stroke and/or cerebral injury." In the first place, Applicants dispute this very general statement. For example, no relevance of NCAM or VEGF to the "measurement of" stroke or cerebral injury has been shown. Further, and importantly, Applicants note that the present claims do not relate to the use of markers "in the measurement of" stroke and/or cerebral injury. Rather, the present claims are very specific in reciting methods for assigning a risk of future cerebral vasospasm in a subject suffering from a subarachnoid hemorrhage. In addition, Applicants disagree that the invention provides a "combination of multiple markers to produce a predictable result". This statement is unsubstantiated, as no articulated reasoning is provided for *why* a correlation of the presence or amount of the recited markers with a risk of a cerebral vasospasm occurring in the future in a patient suffering from subarachnoid hemorrhage is a "predictable result".

Because all features of claim 18 are not present in the cited references, and no rational basis for the claimed invention is present, Applicants assert that claim 18 is nonobvious under U.S.C. § 103(a) and respectfully request that the rejection be reconsidered and withdrawn.

VII. Applicants respectfully traverse the rejection of claim 25 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sviri *et al.*, discussed above, in view of Montaner *et al.*, *Stroke* 32: 1759-66, 2001. Applicants respectfully submit that the conditions for a rejection based on obviousness have not been met for at least the following reasons.

Sviri *et al.* does not disclose or suggest correlating the presence or amount of a plurality of markers that includes MMP-9 for determining the risk of a future cerebral vasospasm in a subject who has suffered a subarachnoid hemorrhage, as provided in claim 1, from which claim 25 depends. Montaner *et al.* does not remedy the deficiencies of Sviri *et al.*, in that Montaner *et al.* makes no mention of the risk of vasospasm following cerebral hemorrhage, and does not disclose correlating the presence or amount of a plurality of markers that includes MMP-9 to a risk of a future cerebral vasospasm in subject that has suffered subarachnoid hemorrhage, as required by the claims.

Further, no rationale is provided for the alleged obviousness of invention as claimed. The Applicants respectfully submit that the statement in the Office Action that Montaner et al. "demonstrated an association between MMP-9 over expression and stroke severity, infarct size, and the time and location of MCA (middle cerebral artery) occlusion" has no relevance to the claimed invention, which concerns assessing the risk of future cerebral vasospasm after subarachnoid hemorrhage. The Office Action further states: "Montaner et al. taught that ELISA measurements of MMPs for stroke patients seem to be a good tool for research. . . As well as the deleterious role of MMP-9 in the development of brain damage after human ischemic stroke." The claimed invention neither seeks to provide research tools nor aims to assess brain damage after ischemic stroke. No reasoning is provided for the alleged obviousness of the claimed invention, which is drawn to correlating the presence or amount of a plurality of markers that includes MMP-9 to a risk of a future cerebral vasospasm in subject that has suffered subarachnoid hemorrhage (claim 25).

Because all features of claim 25 are not present in the cited references, and a rationale for providing the invention of claim 25 is not present, Applicants respectfully request that the rejection of claim 25 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

VIII. Applicants respectfully traverse the rejection of claim 26 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sviri *et al.*, discussed above, in view of Liu *et al.*, *Thrombosis Res.* 72: 353-358, 1993. Applicants assert that claim 26 is nonobvious over the cited references for at least the following reasons.

Sviri *et al.* does not disclose or suggest correlating the presence or amount of a plurality of markers that includes vWF for determining the risk of a future cerebral vasospasm in a subject who has suffered a subarachnoid hemorrhage, as provided in claim 26. Liu *et al.* also fails to provide a method in which the presence or amount of a plurality of biomarkers that includes von Willebrand Factor (vWF) are correlated with the risk of cerebral vasospasm following subarachnoid hemorrhage. Further, no rationale is present for detecting the presence or amount of a plurality of markers that include vWF and correlating the results with a risk of a future cerebral vasospasm in patients that have suffered subarachnoid hemorrhage

The Office Action states: that "Liu *et al.* demonstrated that vWF levels are increased in both thrombotic and hemorrhagic stroke" and ". . . the substitution of one known element (marker) for another would have yielded predictable results (correlation to stroke) . . ." With regard to the first statement, no reasoning is provided as to why a marker whose level is increased in patients that have *already* suffered either thrombotic or hemorrhagic stroke would be considered useful in assessing a risk of a *future* cerebral vasospasm in patients suffering from hemorrhagic stroke. With regard to the second statement, in stating that the "predictable result" is "correlation to stroke", the Office Action fails to address the claimed invention, which does not correlate anything with a stroke that has already occurred.

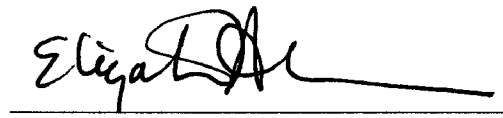
Because all elements of claim 26 are not present in the references cited, and no rationale is present for providing the invention of claim 26, the requirements for the rejection of claim 26 under 35 U.S.C. § 103(a) are not met. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claim 26.

CONCLUSION

Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI



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